

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
6 October 2005 (06.10.2005)

PCT

(10) International Publication Number
WO 2005/092123 A1

- (51) International Patent Classification⁷: **A23L 1/30**, A61K 31/122, 31/205
- (21) International Application Number: PCT/US2005/004781
- (22) International Filing Date: 16 February 2005 (16.02.2005)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
10/792,648 3 March 2004 (03.03.2004) US
- (71) Applicant (for all designated States except US): **SOFT GEL TECHNOLOGIES, INC.** [US/US]; 6982 Bandini Boulevard, Los Angeles, CA 90040 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **FANTUZZI, Michael** [US/US]; 1421 Rock Glen Avenue, Apt. C, Glendale, CA 91205-2018 (US). **UDELL, Ronald, G.** [US/US]; 527 Hillgreen Drive, Beverly Hills, CA 90212 (US).
- (74) Agents: **ROTHENBERGER, Scott, D.** et al.; Dorsey & Whitney LLP, Intellectual Property Department, Suite 1500, 50 South Sixth Street, Minneapolis, MN 55402-1498 (US).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: SOLUBILIZED COQ-10 AND CARNITINE

(57) Abstract: The present invention is directed to compositions and methods of delivery of CoQ-10 and an amino acid solubilized in monoterpenes. Use of monoterpenes as dissolving agents, greatly effects the ability to incorporate greater amounts of bioactive CoQ-10 and the amino acid, such as carnitine, i.e., carnitine tartrate, in formulations, such as soft gel capsules.



WO 2005/092123 A1

SOLUBILIZED COQ-10 AND CARNITINE

CROSS-REFERENCE TO RELATED APPLICATION(S)

[001] This application claims priority to US Application No. 10/674,268, filed on September 29, 2003 (attorney docket number 33503/US), entitled "Solubilized CoQ-10", and also US Application No. 10/792,648, filed on March 3, 2004 (attorney docket number 33503/US/2), entitled "Solubilized CoQ-10 and Carnitine", the contents of which are incorporated herein in their entirety by reference.

FIELD OF THE INVENTION

[002] The present invention relates to the solubilization of coenzyme Q-10 and analogs thereof and/or carnitine and analogs thereof in at least one monoterpene, thereby providing increased bioavailability in delivery.

BACKGROUND OF THE INVENTION

[003] CoQ-10 (coenzyme Q10) is a fat-soluble quinone that is structurally similar to vitamin K and commonly known as ubiquinone. CoQ-10 is found in most living organisms, and is essential for the production of cellular energy. CoQ-10 (2,3 dimethyl-5 methyl-6-decaprenyl benzoquinone) is an endogenous antioxidant found in small amounts in meats and seafood. Although CoQ-10 is found in all human cells, the highest concentrations of CoQ-10 occur in the heart, liver, kidneys, and pancreas. It is found naturally in the organs of many mammalian species.

[004] CoQ-10 can be synthesized in the body or it can be derived from dietary sources. Situations may arise, however, when the need for CoQ-10 surpasses the body's ability to synthesize it. CoQ-10 can be absorbed by oral supplementation as evidenced by significant increases in serum CoQ-10 levels after supplementation.

[005] CoQ-10 is an important nutrient because it lies within the membrane of a cell organelle called the mitochondria. Mitochondria are known as the "power house" of the cell because of their ability to produce cellular energy, or ATP, by shuttling protons derived from nutrient breakdown through the process of aerobic (oxygen) metabolism. CoQ-10 also has a secondary role as an antioxidant. CoQ-10, due to the involvement in ATP synthesis, affects the function of almost all cells in the body, making it essential for the health of all human tissues and organs. CoQ-10 particularly effects the cells that are the most metabolically active: heart, immune system, gingiva, and gastric mucosa

[006] Several clinical trials have shown CoQ-10 to be effective in supporting blood pressure and cholesterol levels. Furthermore, CoQ-10 has also been shown to improve cardiovascular health. CoQ-10 has been implicated as being an essential component in thwarting various diseases such as certain types of cancers. These facts lead many to believe that CoQ-10 supplementation is vital to an individual's well being.

[007] CoQ-10 is sparingly soluble in most hydrophilic solvents such as water. Therefore, CoQ-10 is often administered in a powdered form, as in a tablet or as a suspension. However, delivery of CoQ-10 by these methods limits the bioavailability of the material to the individual.

[008] Carnitine is a water-soluble vitamin like compound that the body utilizes to turn fat into energy. Carnitine works as part of an enzymatic complex formed from carnitine acyltransferase 1, carnitine translocase and carnitine transferase 11.

[009] Carnitine is often used for heart conditions and it may be useful to treat angina or chest pain. Research has also shown that carnitine is also useful in the treatment of congestive heart failure and intermittent claudication. Although carnitine does not increase blood flow, it is believe that it helps muscles to better function under difficult painful circumstances, such as those associated with claudication.

[010] The actions of carnitine and CoQ-10 are interrelated. In fact, carnitine, through beta-oxidation of fatty acids, is able to restore the energy supplies necessary for cell-life, whereas Coenzyme Q is able to restore the ATP supplies necessary for the energetic metabolic processes of the cell.

[011] There is a need in the art for an improved methodology to deliver increased amounts of bioavailable CoQ-10 and/or an amino acid, such as carnitine to an individual in need thereof.

BRIEF SUMMARY OF THE INVENTION

[012] The present invention pertains to the surprising discovery that ubiquinone (CoQ-10) and an amino acid such as carnitine can be readily dissolved in varying concentrations in a monoterpene. Generally, until the present discovery, most liquid delivery methods used for either CoQ-10 and/or an amino acid such as carnitine could solubilize only up to about 5% by weight of the CoQ-10 in the "solvent". Typical solvents included various oils or the combination of CoQ-10 and amino acid(s) was held in an aqueous suspension. The present invention provides the ability to solubilize both CoQ-10 and/or an amino acid such as carnitine in at least one monoterpene in concentrations of up to about 60% (weight to weight) without the need to aggressively heat the solution or with gentle warming. In particular, the solubilization of the CoQ-10 and/or amino acid with a monoterpene can be accomplished at ambient temperatures.

[013] In one aspect, the present invention pertains to compositions that include coenzyme Q-10 or an analog thereof and/or an amino acid (or analog thereof, i.e., carnitine) with a sufficient quantity of a monoterpene that is suitable to solubilize said coenzyme Q-10, and/or an amino acid and, optionally, a pharmaceutically acceptable carrier. Generally, about 30 to about 45% of the CoQ-10 (by weight) is solubilized in the monoterpene and between about 0.5% to about 20% of the amino acid is solubilized (by weight) in the monoterpene. In particular, the range of the amino acid, such as a carnitine, is between about 0.2 to

about 15%, more particularly, between about 0.5 and 10%, and even more particularly, between about 1.0% and about 2.0% (by weight of amino acid). In one particular aspect, the monoterpene is limonene. The compositions of the invention are useful as dietary supplements or as nutraceuticals.

[014] In particular, the compositions of the invention are included in a soft gelatin (soft gel) capsule. Typically, the soft gelatin capsule includes at least 5% by weight of coenzyme Q-10 or an analog thereof and/or at least about 1.5 to about 2% by weight of an amino acid, i.e., carnitine or an analog thereof, solubilized in at least one monoterpene. Typical monoterpenes include, for example, perillyl alcohol, perillic acid, cis-dihydroperillic acid, trans-dihydroperillic acid, methyl esters of perillic acid, methyl esters of dihydroperillic acid, limonene-2-diol, uroterpenol, and combinations thereof.

[015] In another embodiment, the present invention pertains to methods for delivery of an effective amount of bioavailable CoQ-10 and/or an amino acid, such as carnitine, to an individual. The method includes providing CoQ-10 and/or an amino acid solubilized in a monoterpene, such that an effective amount of CoQ-10 and/or an amino acid is provided to the individual.

[016] In still another embodiment, the present invention also includes packaged formulations of the invention that include at least one monoterpene as a solvent for CoQ-10 and/or an amino acid and instructions for use of the tablet, capsule, elixir, etc.

[017] While multiple embodiments are disclosed, still other embodiments of the present invention will become apparent to those skilled in the art from the following detailed description, which shows and describes illustrative embodiments of the invention. As will be realized, the invention is capable of modifications in various obvious aspects, all without departing from the spirit and scope of the present invention. Accordingly, the drawings and detailed description are to be regarded as illustrative in nature and not restrictive.

DETAILED DESCRIPTION

[018] The present invention pertains to the surprising discovery that ubiquinone (CoQ-10) and/or an amino acid such as carnitine can be readily dissolved in varying concentrations in various monoterpenes. CoQ-10 is found in most living organisms, and is essential for the production of cellular energy. Ubiquinone is a naturally occurring hydrogen carrier in the respiratory chain (coenzyme Q) and structurally, it is a 2,3-dimethoxy-5-methyl-1, 4-benzoquinone with a multiprenyl side chain, the number of isoprene units varying depending upon the organism from which it is derived. CoQ-10 analogs include reduced and semi-reduced CoQ-10 and ubiquinone derivatives described, for example, in WO 8803015, the teachings of which are incorporated herein by reference.

[019] L-carnitine is recognized in the art and facilitates transport of materials through the mitochondrial membrane. L-carnitine is an essential fatty acid metabolism cofactor that helps to move fatty acids to the mitochondria from the cytoplasm. This is an important factor as this is where CoQ-10 uptake occurs.

[020] In one aspect of the present invention, L-carnitine is included in soft gel formulations in combination with CoQ-10. Suitable ratios of L-carnitine and CoQ-10 are known in the art and include those described in US Patent No. 4,599,232, issued to Sigma Tau Industrie Faramaceutiche Riunite S.p.A. on July 8, 1986, the teachings of which are incorporated herein in their entirety. In particular, combinations of limonene, CoQ-10 and L-carnitine in soft gel formulations are of importance. The present invention provides the advantage of solvating large amounts (relative to that of current state of the art) of CoQ-10 in limonene in a soft gel capsule along with an additive, such as L-carnitine.

[021] It should be understood, that throughout the specification, reference is made to CoQ-10 or amino acids, such as carnitine, and that such reference includes the analogs thereof.

[022] Generally, until the present discovery, most liquid delivery methods could solubilize only up to at most about 10% by weight of the CoQ-10

and/or an amino acid in the "solvent. Typical solvents included oils or, for example, the CoQ-10 was held in an aqueous suspension. Alternatively, the CoQ-10 and/or the amino acid were provided as a solid in a tablet or powder.

[023] The present invention provides the ability to solubilize CoQ-10 and/or amino acids in a monoterpene, as defined herein, in concentrations of up to about 60% (weight to weight) without the need to heat the solution. In one aspect, the monoterpene solubilizes CoQ-10 from about 0.1 percent by weight to about 45 percent by weight.

[024] In particular, the solubilization of the CoQ-10 with monoterpenes can be accomplished at ambient temperatures. In one aspect, from about 5 to about 50 percent (weight CoQ-10/weight solvent) CoQ-10 can be solubilized in a monoterpene. In another aspect, from about 15 to about 40 percent w/w can be solubilized and in still another aspect, from about 20 to about 35 percent w/w CoQ-10 can be solubilized in a monoterpene.

[025] In another aspect, the solubilization of an amino acid or an amino acid analog, such as carnitine, with one or more monoterpenes can be accomplished at ambient temperatures. In one aspect, from about 0.05 to about 0.5 percent (weight amino acid/weight solvent) amino acid can be solubilized in a monoterpene. In another aspect, from about 0.01 to about 0.25 percent w/w can be solubilized and in still another aspect, from about 0.02 to about 0.2 percent w/w amino acid can be solubilized in a monoterpene.

[026] The term "amino acid" as used herein includes, but is not limited to, glycine, the L forms of alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, proline, hydroxyproline, serine, threonine, cysteine, cystine, methionine, tryptophan, aspartic acid, glutamic acid, arginine, lysine, histidine, ornithine, hydroxylysine, carnitine, and other naturally occurring amino acids and analogs thereof.

[027] For example amino acid analogs, such as carnitine “analogs” include acetylated products, fumarate derivatives and the like, and acceptable ammonium and metal salts thereof.

[028] The term "carnitine" is also known as 3-Carboxy-2-hydroxy-N,N,N-trimethyl-1-propanaminium hydroxide, inner salt; (3-carboxy-2-hydroxypropyl)trimethylammonium hydroxide, inner salt; gamma-amino-beta-hydroxybutyric acid trimethylbetaine; gamma-trimethyl-beta-hydroxybutyrobetaine; 3-hydroxy-4-(trimethyl-ammonio)butanoate. See The Merck Index (1989), p. 281 and references cited therein. Therefore, "carnitine" and “carnitine analogs” includes, but is not limited to racemic or essentially pure L-carnitine (carnitine), or a corresponding alkanoyl-carnitine such as e.g. acetyl-carnitine or propionyl-carnitine, or a suitable salt of such compounds such as e.g. L-carnitine tartrate, L-carnitine fumarate, L-carnitine-magnesium-citrate, acetyl-L-carnitine tartrate, acetyl-L-carnitine-magnesium-citrate, or any mixture of the afore mentioned compounds.

[029] Carnitine and carnitine analogs also include those described in U.S. Pat. Nos. 5,362,753, 4,687,782, 5,030,458, 5,030,657, 4,343,816, 5,560,928, 5,504,072, 5,391,550 and 5,240,961, the teachings of which are incorporated herein by reference in their entirety.

[030] The phrase “sufficient quantity of a monoterpene suitable to solubilize” is therefore intended to mean that that amount of a monoterpene that will dissolve a component under a given set of conditions, generally, those at ambient temperature. This determination should be understood by one skilled in the art and can be determined by methods known in the art, such as by solubility studies.

[031] One of the particular advantages of utilizing monoterpenes in combination with CoQ-10 and/or an amino acid is that the ingredient is dissolved by the monoterpene. That is, many formulations currently in the marketplace have CoQ-10, for example, present as a suspension; a situation where not all the

CoQ-10 is dissolved. This reduces efficacy and the bioavailability of the CoQ-10 and/or the amino acid (if present). The present invention eliminates this disadvantage by solubilizing the components in the monoterpene.

[032] A particular advantage in using monoterpenes is that the CoQ-10 does not have to be heated to dissolve into solution. This is important so that the CoQ-10 does not degrade upon dissolution.

[033] The term "monoterpene" as used herein, refers to a compound having a 10-carbon skeleton with non-linear branches. A monoterpene refers to a compound with two isoprene units connected in a head-to-end manner. The term "monoterpene" is also intended to include "monoterpenoid", which refers to a monoterpene-like substance and may be used loosely herein to refer collectively to monoterpenoid derivatives as well as monoterpenoid analogs. Monoterpenoids can therefore include monoterpenes, alcohols, ketones, aldehydes, ethers, acids, hydrocarbons without an oxygen functional group, and so forth.

[034] It is common practice to refer to certain phenolic compounds, such as eugenol, thymol and carvacrol, as monoterpenoids because their function is essentially the same as a monoterpenoid. However, these compounds are not technically "monoterpenoids" (or "monoterpenes") because they are not synthesized by the same isoprene biosynthesis pathway, but rather by production of phenols from tyrosine. However, common practice will be followed herein.

[035] Suitable examples of monoterpenes include, but are not limited to, limonene, pinene, citronellol, terpinene, nerol, menthane, carveol, S-linalool, safrol, cinnamic acid, apiol, geraniol, thymol, citral, carvone, camphor, etc. and derivatives thereof. For information about the structure and synthesis of terpenes, including terpenes of the invention, see Kirk-Othmer Encyclopedia of Chemical Technology, Mark, et al., eds., 22:709-762 3d Ed (1983), the teachings of which are incorporated herein in their entirety.

[036] In particular, suitable limonene derivatives include perillyl alcohol, perillic acid, cis-dihydroperillic acid, trans-dihydroperillic acid, methyl esters of

perillic acid, methyl esters of dihydroperillic acid, limonene-2-diol, uroterpenol, and combinations thereof.

[037] Formulation of the CoQ-10 and/or an amino acid can be accomplished by many methods known in the art. For example, the solubilized CoQ-10 can be formulated in a suspension, an emulsion, an elixir, a solution, a caplet that harbors the liquid, or in a soft gelatin capsule. Often the formulation will include an acceptable carrier, such as an oil, or other suspending agent.

[038] Suitable carriers include but are not limited to, for example, fatty acids, esters and salts thereof, that can be derived from any source, including, without limitation, natural or synthetic oils, fats, waxes or combinations thereof. Moreover, the fatty acids can be derived, without limitation, from non-hydrogenated oils, partially hydrogenated oils, fully hydrogenated oils or combinations thereof. Non-limiting exemplary sources of fatty acids (their esters and salts) include seed oil, fish or marine oil, canola oil, vegetable oil, safflower oil, sunflower oil, nasturtium seed oil, mustard seed oil, olive oil, sesame oil, soybean oil, corn oil, peanut oil, cottonseed oil, rice bran oil, babassu nut oil, palm oil, low erucic rapeseed oil, palm kernel oil, lupin oil, coconut oil, flaxseed oil, evening primrose oil, jojoba, tallow, beef tallow, butter, chicken fat, lard, dairy butterfat, shea butter or combinations thereof.

[039] Specific non-limiting exemplary fish or marine oil sources include shellfish oil, tuna oil, mackerel oil, salmon oil, menhaden, anchovy, herring, trout, sardines or combinations thereof. In particular, the source of the fatty acids is fish or marine oil (DHA or EPA), soybean oil or flaxseed oil. Alternatively or in combination with one of the above identified carriers, beeswax can be used as a suitable carrier, as well as suspending agents such as silica (silicon dioxide).

[040] The formulations of the invention are considered dietary supplements useful to the increase the amounts of CoQ-10 and/or amino acid(s) in individuals in need thereof.

[041] Alternatively, the formulations of the invention are also considered to be nutraceuticals. The term “nutraceutical” is recognized in the art and is intended to describe specific chemical compounds found in foods that may prevent disease. CoQ-10 and amino acids are such compounds.

[042] The formulations of the invention can further include various ingredients to help stabilize, or help promote the bioavailability of the CoQ-10 and/or amino acid(s), or serve as additional nutrients to an individual's diet. Suitable additives can include vitamins and biologically-acceptable minerals. Non-limiting examples of vitamins include vitamin A, B vitamins, vitamin C, vitamin D, vitamin E, vitamin K and folic acid. Non-limiting examples of minerals include iron, calcium, magnesium, potassium, copper, chromium, zinc, molybdenum, iodine, boron, selenium, manganese, derivatives thereof or combinations thereof. These vitamins and minerals may be from any source or combination of sources, without limitation. Non-limiting exemplary B vitamins include, without limitation, thiamine, niacinamide, pyridoxine, riboflavin, cyanocobalamin, biotin, pantothenic acid or combinations thereof.

[043] Vitamin(s), if present, are present in the composition of the invention in an amount ranging from about 5 mg to about 500 mg. More particularly, the vitamin(s) is present in an amount ranging from about 10 mg to about 400 mg. Even more specifically, the vitamin(s) is present from about 250 mg to about 400 mg. Most specifically, the vitamin(s) is present in an amount ranging from about 10 mg to about 50 mg. For example, B vitamins are in usually incorporated in the range of about 1 milligram to about 10 milligrams, i.e., from about 3 micrograms to about 50 micrograms of B12. Folic acid, for example, is generally incorporated in a range of about 50 to about 400 micrograms, biotin is generally incorporated in a range of about 25 to about 700 micrograms and cyanocobalamin is incorporated in a range of about 3 micrograms to about 50 micrograms.

[044] Mineral(s), if present, are present in the composition of the invention in an amount ranging from about 25 mg to about 1000 mg. More particularly, the mineral(s) are present in the composition ranging from about 25 mg to about 500 mg. Even more particularly, the mineral(s) are present in the composition in an amount ranging from about 100 mg to about 600 mg.

[045] Various additives can be incorporated into the present compositions. Optional additives of the present composition include, without limitation, phospholipids, L-carnitine, starches, sugars, fats, antioxidants, amino acids, proteins, flavorings, coloring agents, hydrolyzed starch(es) and derivatives thereof or combinations thereof.

[046] As used herein, the term "phospholipid" is recognized in the art, and refers to phosphatidyl glycerol, phosphatidyl inositol, phosphatidyl serine, phosphatidyl choline, phosphatidyl ethanolamine, as well as phosphatidic acids, ceramides, cerebroside, sphingomyelins and cardiolipins.

[047] As used herein, the term "antioxidant" is recognized in the art and refers to synthetic or natural substances that prevent or delay the oxidative deterioration of a compound. Exemplary antioxidants include tocopherols, flavonoids, catechins, superoxide dismutase, lecithin, gamma oryzanol; vitamins, such as vitamins A, C (ascorbic acid) and E and beta-carotene; natural components such as camosol, carnosic acid and rosmanol found in rosemary and hawthorn extract, proanthocyanidins such as those found in grapeseed or pine bark extract, and green tea extract.

[048] The term "flavonoid" as used herein is recognized in the art and is intended to include those plant pigments found in many foods that are thought to help protect the body from cancer. These include, for example, epi-gallo catechin gallate (EGCG), epi-gallo catechin (EGC) and epi-catechin (EC).

[049] Any dosage form, and combinations thereof, are contemplated by the present invention. Examples of such dosage forms include, without limitation, chewable tablets, elixirs, liquids, solutions, suspensions, emulsions, capsules, soft

gelatin capsules, hard gelatin capsules, caplets, lozenges, chewable lozenges, suppositories, creams, topicals, ingestibles, injectables, infusions, health bars, confections, animal feeds, cereals, cereal coatings, and combinations thereof. The preparation of the above dosage forms are well known to persons of ordinary skill in the art.

[050] For example, health bars can be prepared, without limitation, by mixing the formulation plus excipients (e.g., binders, fillers, flavors, colors, etc.) to a plastic mass consistency. The mass is then either extended or molded to form "candy bar" shapes that are then dried or allowed to solidify to form the final product.

[051] Soft gel or soft gelatin capsules can be prepared, for example, without limitation, by dispersing the formulation in an appropriate vehicle (e.g. rice bran oil, monoterpene and/or beeswax) to form a high viscosity mixture. This mixture is then encapsulated with a gelatin based film using technology and machinery known to those in the soft gel industry. The industrial units so formed are then dried to constant weight. Typically, the weight of the capsule is between about 100 to about 2500 milligrams and in particular weigh between about 1500 and about 1900 milligrams, and more specifically can weigh between about 1500 and about 2000 milligrams.

[052] For example, when preparing soft gelatin shells, the shell can include between about 20 to 70 percent gelatin, generally a plasticizer and about 5 to about 60% by weight sorbitol. The filling of the soft gelatin capsule is liquid (principally limonene, in combination with rice bran oil and/or beeswax if desired) and can include, apart from the antioxidant actives, a hydrophilic matrix. The hydrophilic matrix, if present, is a polyethylene glycol having an average molecular weight of from about 200 to 1000. Further ingredients are optionally thickening agents. In one embodiment, the hydrophilic matrix includes polyethylene glycol having an average molecular weight of from about 200 to

1000, 5 to 15% glycerol, and 5 to 15% by weight of water. The polyethylene glycol can also be mixed with propylene glycol and/or propylene carbonate.

[053] In another embodiment, the soft gel capsule is prepared from gelatin, glycerine, water and various additives. Typically, the percentage (by weight) of the gelatin is between about 30 and about 50 weight percent, in particular between about 35 and about weight percent and more specifically about 42 weight percent. The formulation includes between about 15 and about 25 weight percent glycerine, more particularly between about 17 and about 23 weight percent and more specifically about 20 weight percent glycerine.

[054] The remaining portion of the capsule is typically water. The amount varies from between about 25 weight percent and about 40 weight percent, more particularly between about 30 and about 35 weight percent, and more specifically about 35 weight percent. The remainder of the capsule can vary, generally, between about 2 and about 10 weight percent composed of a flavoring agent(s), sugar, coloring agent(s), etc. or combination thereof. After the capsule is processed, the water content of the final capsule is often between about 5 and about 10 weight percent, more particularly 7 and about 12 weight percent, and more specifically between about 9 and about 10 weight percent.

[055] As for the manufacturing, it is contemplated that standard soft shell gelatin capsule manufacturing techniques can be used to prepare the soft-shell product. Examples of useful manufacturing techniques are the plate process, the rotary die process pioneered by R. P. Scherer, the process using the Norton capsule machine, and the Accogel machine and process developed by Lederle. Each of these processes are mature technologies and are all widely available to any one wishing to prepare soft gelatin capsules.

[056] Typically, when a soft gel capsule is prepared, the total weight is between about 250 milligrams and about 2.5 gram in weight, e.g., 400-750 milligrams. Therefore, the total weight of additives, such as vitamins and antioxidants, is between about 80 milligrams and about 2000 milligrams,

alternatively, between about 100 milligrams and about 1500 milligrams, and in particular between about 120 milligrams and about 1200 milligrams. In particular, the soft gel capsule typically weighs between about 1000 milligrams and 1300 milligrams, wherein the percentage fill is about 50% of the entire weight of the capsule, i.e., from about 500 to about 650 milligrams fill weight. The fill weight includes the active ingredient(s), solubilizing agents, etc.

[057] Preparation of the soft gel capsules was accomplished by methods well known in the art including, but not limited to those described throughout the specification and in US Patent Nos. 6,616,942, 6,623,734 and pending US Serial Nos. 10/035,753 and 09/825,920, the contents of which are incorporated herein by reference in their entirety.

[058] For example, a soft gel capsule can be prepared by mixing a 35% solution of CoQ-10 (by weight) and a 26% solution of an amino acid, such as carnitine (by weight), and limonene (w/w/w) (e.g., 104 milligrams of CoQ-10, 228 milligrams carnitine tartrate in 470.5 milligrams of limonene) with between about 0.01 grams and about 0.4 grams (e.g., 0.1 grams) tocopherol, between about 200 grams and about 250 grams (e.g., 225 grams) rice bran oil and between about 0.01 grams and about 0.5 grams betacarotene (e.g. about 0.02 grams). The mixture is then combined with encapsulated within a gelatin capsule as described above.

[059] The present invention also provides packaged formulations of a monoterpene with CoQ-10 and/or an amino acid such as carnitine and instructions for use of the tablet, capsule, elixir, etc. Typically, the packaged formulation, in whatever form, is administered to an individual in need thereof that requires an increase in the amount of CoQ-10 and/or the amino acid in the individual's diet. Typically, the dosage requirement is between about 1 to about 4 dosages a day.

[060] CoQ-10 has been implicated in various biochemical pathways and is suitable for the treatment of cardiovascular conditions, such as those associated with, for example, statin drugs that effect the body's ability to product CoQ-10

naturally. CoQ-10 has also been implicated in various periodontal diseases. Furthermore, CoQ-10 has been implicated in mitochondrial related diseases and disorders, such as the inability to product acetyl coenzyme A, neurological disorders, for example, such as Parkinson's disease and, Prater-Willey syndrome.

[061] The following examples are intended to be illustrative only and should not be considered limiting.

[062] **Examples**

[063] Formulations of CoQ-10 and an amino acid, such as carnitine, can be prepared in the following ratios by mixing the components together and then placing into a soft gel capsule.

<u>Component</u>	<u>Example 1</u>	<u>Example 2</u>
CoQ-10	104.09 mg	104.09 mg
Carnitine tartrate	227.69 mg	196.02 mg
Mixed Tocopherols	269.03 mg	269.03 mg
(372 IU/g)		
Rice Bran Oil	176.02 mg	0
Natural Beta Carotene	10.05 mg	10.05 mg
(20% by weight)		
Yellow Beeswax	20.0 mg	0
D-limonene	0 mg	227.69 mg
Total weight	796 mg	796 mg

[064] Example 2 demonstrates that the use of limonene solubilizes CoQ-10 and carnitine tartrate without the requirement of beeswax and/or rice bran oil

being present. Examples 1 and 2 could be incorporated into soft gel capsules by standard methods known in the art and as described herein.

<u>Component</u>	<u>Example 3</u>	<u>Example 4</u>
CoQ-10	104.08 mg	104.08 mg
Carnitine (tartrate)	4.50 mg	78 mg
D-Limonene	191.42 mg	167.92 mg
5-67 Tocopherol	50 mg (50 IU)	100 mg (100 IU)

[065] Examples 3 and 4 demonstrate that CoQ-10 and carnitine tartrate can be solubilized in scalable quantities. Additives, such as EPAX 2050 TG (an ω -3 oil; 20% EPA/50% DHA as triglycerides, remainder fatty acid/triglycerides; Pronova Biocare) and tocopherols (5-67 Tocopherol; BD Industries) can easily be incorporated into such limonene containing formulations. The resultant mixtures contained approximately 100 mg of CoQ-10 and ranges of carnitine (based on carnitine tartrate) per soft gel capsule. Preparation of the soft gel capsules was accomplished by methods well known in the art and as described herein.

[066] Although the present invention has been described with reference to preferred embodiments, persons skilled in the art will recognize that changes may be made in form and detail without departing from the spirit and scope of the invention.

[067] All literature and patent references cited throughout the application are incorporated by reference into the application for all purposes.

Claims

What is claimed is:

1. A composition comprising:
coenzyme Q-10 and an amino acid or analogs thereof;
a sufficient quantity of at least one monoterpene suitable to
solubilize said coenzyme Q-10 and amino acid; and
an acceptable carrier.
2. The composition of claim 1, wherein said coenzyme Q-10 or an analog thereof is selected from the group consisting of coenzyme Q-10, reduced coenzyme Q-10 and semi-reduced coenzyme Q-10.
3. The composition of claim 1, wherein said at least one monoterpene is limonene or a derivative thereof.
4. The composition of claim 3, wherein said limonene derivatives are selected from the group consisting of perillyl alcohol, perillic acid, cis-dihydroperillic acid, trans-dihydroperillic acid, methyl esters of perillic acid, methyl esters of dihydroperillic acid, limonene-2-diol, uroterpenol, and combinations thereof.
5. The composition of claim 1, wherein said composition is in the form of a solution, an elixir, a suspension, or a caplet.
6. The composition of claim 5, wherein said caplet is a soft gelatin tablet.
7. The composition of claim 6, wherein said soft gelatin tablet further comprises rice bran oil or beeswax.

8. The composition of claim 1, wherein said coenzyme Q-10 or analog thereof is solubilized in said at least one monoterpene in an amount of at least about 0.1 % by weight to about 45% by weight.
9. The composition of claim 1, wherein said coenzyme Q-10 or analog thereof is solubilized in said monoterpene in an amount of least about 5% to about 40% by weight.
10. The composition of claim 1, wherein said amino acid is carnitine or an analog thereof.
11. The composition of claim 10, wherein said carnitine or an analog thereof is solubilized in said at least one monoterpene in an amount of at least about 0.1 % by weight to about 20 % by weight.
12. The composition of claim 10, wherein said carnitine or an analog thereof is solubilized in said at least one monoterpene in an amount of at least about 0.5 % by weight to about 10 % by weight.
13. The composition of claim 1, further comprising vitamin E.
14. The composition of claim 1, further comprising a seed oil.
15. The composition of claim 1, further comprising a fish oil.
16. The composition of claim 1, further comprising an antioxidant.
17. A soft gelatin capsule, comprising
at least 5% by weight of coenzyme Q-10 and 0.5% of an amino acid or analogs thereof solubilized in at least one monoterpene.

18. The soft gelatin capsule of claim 17, wherein said coenzyme Q-10 or analog thereof is selected from the group consisting of coenzyme Q-10, reduced coenzyme Q-10 and semi-reduced coenzyme Q-10.
19. The soft gelatin capsule of claim 17, wherein said monoterpene is limonene or a derivative thereof.
20. The soft gelatin capsule of claim 19, wherein said limonene derivative is selected from the group consisting of perillyl alcohol, perillic acid, cis-dihydroperillic acid, trans-dihydroperillic acid, methyl esters of perillic acid, methyl esters of dihydroperillic acid, limonene-2-diol, uroterpenol, and combinations thereof.
21. The soft gelatin capsule of claim 17, wherein said coenzyme Q-10 is solubilized in said at least one monoterpene in an amount of about 10 percent to about 40 percent by weight.
22. The soft gelatin of claim 17, wherein said soft gelatin tablet further comprises rice bran oil or beeswax.
23. The soft gelatin of claim 17, wherein said soft gelatin tablet further comprises an antioxidant.
24. The soft gelatin of claim 17, wherein said amino acid is carnitine or an analog thereof.
25. The soft gelatin of claim 24, wherein said carnitine or an analog thereof is solubilized in said at least one monoterpene in an amount of at least about 0.1 % by weight to about 20 % by weight.

26. The soft gelatin of claim 24, wherein said carnitine or an analog thereof is solubilized in said at least one monoterpene in an amount of at least about 0.5 % by weight to about 10 % by weight.

27. A method for the delivery of an effective amount of bioavailable coenzyme Q-10 and an amino acid to an individual in need thereof, comprising the steps of

providing coenzyme Q-10 and an amino acid solubilized in at least one monoterpene and an acceptable carrier, such that an effective amount of coenzyme Q-10 is provided to an individual.

28. A packaged nutraceutical formulation comprising:

coenzyme Q-10 and an amino acid or analogs thereof, and a sufficient quantity of a monoterpene suitable to solubilize said coenzyme Q-10 and amino acid, wherein said formulation is encapsulated in a gelatin capsule; and

instructions for use thereof.

29. The packaged nutraceutical formulation of claim 28, wherein said coenzyme Q-10 or an analog thereof is selected from the group consisting of coenzyme Q-10, reduced coenzyme Q-10 and semi-reduced coenzyme Q-10.

30. The packaged nutraceutical formulation of claim 22, wherein said at least one monoterpene is limonene or a derivative thereof.

31. The packaged nutraceutical formulation of claim 29, wherein said amino acid is carnitine or an analog thereof.

32. The packaged nutraceutical formulation of claim 31, wherein said carnitine or an analog thereof is solubilized in said at least one monoterpene in an amount of at least about 0.1 % by weight to about 20 % by weight.

33. The packaged nutraceutical formulation of claim 31, wherein said carnitine or an analog thereof is solubilized in said at least one monoterpene in an amount of at least about 0.5 % by weight to about 10 % by weight.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/004781

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A23L1/30 A61K31/122 A61K31/205

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/40086 A (THE RILEY FLETCHER FOUNDATION; FLETCHER, JANE, CLARISSA; RILEY, MICHAEL) 17 September 1998 (1998-09-17) page 82; claims 1,2,8,9	1-9, 13-23, 27-30
X	DATABASE WPI Section Ch, Week 198216 Derwent Publications Ltd., London, GB; Class A96, AN 1982-31657E XP002313489 -& JP 57 042616 A (FREUND SANGYO KK) 10 March 1982 (1982-03-10)	1-9, 13-23, 31-33
Y	abstract	10-12, 24-26, 31-33
	----- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

22 April 2005

Date of mailing of the international search report

03/05/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Smeets, D

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/004781

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/147927 A1 (NAZZAL SAMI ET AL) 7 August 2003 (2003-08-07)	1-9, 13-23, 31-33
Y	claims	10-12, 24-26, 31-33
X	----- WO 02/09685 A (ELSTNER ERICH ; STEIGERWALD ARZNEIMITTELWERK (DE)) 7 February 2002 (2002-02-07)	1-9, 13-23, 27-30
Y	page 8, line 10 - line 35; claims 1,3,4,6,8-10	10-12, 24-26, 31-33
Y	----- US 4 599 232 A (BERTELLI ET AL) 8 July 1986 (1986-07-08) cited in the application column 1, line 24 - column 2, line 32 column 3, line 10 - line 12 claims 1-4 -----	10-12, 24-26, 31-33

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/004781

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9840086	A	17-09-1998	AU 6408298 A EP 0973529 A2 WO 9840086 A2 JP 2001514650 T US 6280751 B1	29-09-1998 26-01-2000 17-09-1998 11-09-2001 28-08-2001
JP 57042616	A	10-03-1982	NONE	
US 2003147927	A1	07-08-2003	WO 03041632 A2	22-05-2003
WO 0209685	A	07-02-2002	DE 10038640 A1 AU 6732401 A BR 0112663 A CA 2411907 A1 CN 1444475 A CZ 20030194 A3 WO 0209685 A1 DE 10192998 D2 EE 200300044 A EP 1305013 A1 JP 2004513077 T MX PA03000718 A NO 20030412 A SK 872003 A3 US 2004047922 A1 ZA 200210123 A	14-02-2002 13-02-2002 24-06-2003 05-12-2002 24-09-2003 14-05-2003 07-02-2002 16-01-2003 15-10-2004 02-05-2003 30-04-2004 04-06-2003 11-02-2003 03-06-2003 11-03-2004 27-05-2003
US 4599232	A	08-07-1986	CH 655005 A5 BE 898918 A2 DE 3405581 A1 DK 72284 A ,B, FR 2543827 A1 GB 2137088 A ,B IT 1170235 B JP 1581515 C JP 2007572 B JP 59186914 A NL 8400488 A ,B, SE 457143 B SE 8400851 A	27-03-1986 16-08-1984 18-10-1984 17-08-1984 12-10-1984 03-10-1984 03-06-1987 11-10-1990 19-02-1990 23-10-1984 17-09-1984 05-12-1988 17-08-1984